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(54) Continuous high-density cell culture system.

(57) A tissue culture plate assembly wherein a plurality identical flat plates are stacked in face to face relationship with growth chambers formed between adjacent plates. A frame is molded about and encloses the edges of all the plates to hermetically seal the edges of the chambers and mechanically interlock the stack of plates.

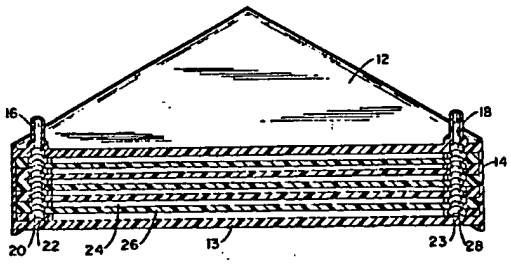

FIG. 2

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This invention relates to a method and apparatus for the culture of cells and more particularly relates to an improvement of the apparatus disclosed in U.S. application Serial No. 07/361,141.

Conventionally, cells have been grown attached to glass or plastic roller bottles and flasks. This approach does not lend itself to high-density growth of cells or continuous cell culture, and requires large amounts of medium and space. Further, this approach is labor intensive.

To achieve higher-density growth conditions, various attempts have been made to use arrangements of stacked plates, the surfaces of the stacked plates providing increased surface area for cell attachment and growth. In spite of the various attempts, the cell-culturing devices of the prior art all have various drawbacks, including the need for excessive amounts of medium, the inability to provide a continuous flow of nutrients to all cell-growth surfaces, the need for labor-intensive monitoring and care of the growing cells and the inability to operate continuously.

An object of this invention is to provide a cell culture device in which cells may be grown to a high density relative to the amount of nutrient medium contained within the system.

Another object of this invention is to provide a cell culture assembly having a plurality of growth chambers for receiving medium flow substantially equally.

Another object of this invention is to provide a cell culture assembly having a plurality of growth chambers, which has reduced manufacturing costs as compared to the system shown in application Serial No. 07/361,141, supra.

Yet another object of this invention is to provide a more effective seal for each of the chambers of the cell culture assembly shown in application Serial No. 07/361,141 supra.

According to the present invention there is provided a tissue culture plate assembly comprising:

a plurality of plates stacked one upon the other with adjacent plates defining growth chambers between them, the plates having edges which are aligned with one another in the stack,

inlet and outlet conduits connected to the stack for channeling fluid to and from the chambers,

and a frame enclosing the edges of all the plates, hermetically sealing the chambers and mechanically interlocking the stacked plates together.

In one aspect the invention may provide a cell culture assembly that allows for the automatic, continuous addition of nutrient medium and the removal of conditioned medium containing the products and waste formed by the cells.

In another aspect the invention may provide a cell culture assembly and system in which the cellular environmental condition may be continuously monitored, with any departures from the desired conditions being automatically corrected or alarmed.

In a further aspect the invention may be arranged to provide a continuous flow system to facilitate a desirable chemostatic environment for the cells and to facilitate optimal yield and harveasing ability for cell products such as biochemicals, vaccine virus, and pharmaceuticals.

The invention provides a continous cell culturing device having an array of growth chambers defining a very large surface area for high-density cell growth in a small volume. The device is constructed and arranged to permit directional flow through the growth chambers, the flow being continuous and capable of reaching all growth surfaces within each chamber. Adequate flow in each chamber is accomplished by providing each chamber with a fluid restriction port, these ports acting to control the flow and distribution of fluid into each of the growth chambers.

Preferably, the cell culturing device includes an array of cell growth chambers defined by the spaces between a plurality of stacked plates. An inlet conduit provides a source of nutrient medium to a manifold in fluid communication with the cell growth chambers via the fluid restriction ports. The sum of the cross-sectional areas of the narrowest region of the fluid restriction ports is less than the cross-sectional area of the inlet conduit, thereby ensuring a pressure drop across each of the fluid restriction ports and adequate flow of fluid through each growth chamber.

Preferably, the fluid restriction ports and growth chambers are constructed and arranged to promote the distribution and continuous directional flow of fluid medium to all growth surfaces with a minimum of turbulence. This may be accomplished by providing growth chambers that are essentially square boxes, with an inlet restriction port and an outlet restriction port at opposing corners of the box. The fluid restriction ports may have a constricted intermediate section, and the corners may have curved surfaces to promote fluid distribution and nonturbulent flow. Ribs may be provided between opposing faces of the plates to provide structural support and further to direct fluid flow.

The invention thus can provide a closed sterile system for the culture of cells and prevents both exposure of personnel to the cells and their products and the contamination of the culture from the outside environment. Growth conditions may be sensed automatically, with nutrients added and cell-products removed responsive to the sensed condition. The device can be supplied economically and can be manufactured in large scale production.

In a preferred embodiment of the present application, the stacked plates are sealed by a continuous frame that engages the edges of all the plates to seal the chambers. The frame can be molded about the plates as a single step and avoids the handling of the individual plates to separately seal the individual

chambers. Because the assembly may have as many as twenty-five or fifty chambers formed by a corresponding number of plates stacked one upon another, this manufacturing procedure results in very substantial cost savings.

Brief Description of the Drawings

FIG. 1 is a perspective view from the top right of the cell culture assembly of the invention;
FIG. 2 is a perspective cross-sectional view taken along line a-a of Fig. 1;
FIG. 3 is a perspective view from the top front of a single culture plate which may be used in forming the cell culture assembly of Fig. 1;
FIG. 4 is an enlarged view of a corner of the plate of Fig. 3;
FIG. 5 is a perspective view of a cylindrical embodiment of a cell culture vessel assembly of the invention, with a portion of the near side of the broken away casing to show the surface and end of the enclosed growth chamber;
FIG. 6 is an end view in cross-section of the spiralled growth chamber of Fig. 5;
FIG. 7 is a schematic view of a cell culture system vessel assembly of the invention in a continuous cell culture assembly.
FIG. 8 is an exploded front view of a second embodiment of a plate assembly, with a gasket defining the height and configuration of the space between plates which may be used in forming the culture vessel assembly of Fig. 1;
FIG. 9 is a perspective view of another embodiment of cell culture assembly constructed in accordance with this invention;
FIG. 10 is a fragmentary cross-section view of the assembly taken along the section line b-b in FIG. 9;
FIGS. 11 and 12 are plan views of the two faces of one of the many identical plates used in the assembly of FIGS. 9 and 10;
FIGS. 13-15 are fragmentary cross-sectional views of the plates taken along the section line c-c, d-d and e-e, respectively, in FIG. 11; and
FIGS. 16 and 17 are fragmentary cross-sectional views of the plan taken along the section lines f-f and g-g, respetively, in FIG. 12.

Detailed Description

The cell culture device of the present invention embodiment includes an array of growth chambers enclosed within a vessel. The growth chambers provide a large surface area for cell growth. In xterior view (Fig. 1), the vessel 10 is a substantially square box with square, mold d t p 12 and base 13, and v rtical molded sid walls 14 sealed al ng the edges to provide a fluid-tight arrangem nt for housing th growth chambers. Extending from diagonally opposed corners of the top 12, are an inlet conduit 16 and an outlet conduit 18. The inlet conduit 16 provides fluid access to the interior space of the vessel 10, and the outlet conduit 18 provides fluid egress from the interior space of the vessel 10. The outlet conduit 18 may extend through the base 13, rather than through the top 12 as shown.

Referring to Fig. 2, the inlet conduit 16 is in axial alignment and in fluid communication with an inlet manifold 20 extending transversely through the interior space of the vessel 10 at the corner. Inlet restriction ports 22 provide fluid communication between the manifold 20 and a plurality of cell growth chambers 24 located within vessel 10, which chambers 24 are defined by an array of stacked plates 26. At the corner of the vessel opposite the inlet manifold 20 is an outlet manifold 28 in fluid communication with the outlet conduit 18. Each growth chamber 24 is in fluid communication with the outlet manifold 28 via an outlet fluid restriction port 23. The inlet and outlet manifold arrangements in accordance with one embodiment are mirror images of one another and, therefore, the flow characteristics will be the same whether the fluid medium is flowing from the inlet to the outlet ends, or vice versa.

The relative size of the restriction ports 22,23 and conduits 16,18 comprise one aspect of the invention. To ensure that each chamber receives a continuous and controlled flow of fluid medium, a pressure drop must be created across the flow restriction port controlling flow within each chamber. To achieve this, the sizes of the restriction ports controlling flow are selected such that the sum of the cross-sectional areas of the narrowest portion of these restriction ports is equal to or preferably less than the cross-sectional area of the inlet conduit. Preferably, the sum of these cross-sectional areas also is equal to or less than the cross-sectional area of the outlet conduit. When these conditions are present, no particular growth chamber will be favored due to its location, and all growth chambers will receive fluid medium based principally upon the particular size of the fluid restriction port controlling flow in that chamber. Preferably, the fluid restriction ports are uniformly dimensioned so that each growth chamber will receive fluid medium at an identical flow rate.

In the embodiment of FIGS. 2-4, there are flow restriction ports at both the inlet and the outlet end of the growth chambers. The smaller of the inlet and outlet restriction ports will control the flow through a particular growth chamber, without regard to its location at the inlet or outlet end. Thus, it is the sum of the cross-sectional areas of the small r of the inlet and outl t restriction ports f r ach chamber that should be less than th cross-secti nal area of the conduits. If a pair of inlet and outlet restricti n p rts are uniformly dimensi ned and hav th same cross-sec-

ti nal area at their narrowest portion, then in calculating the sum f the cross-sectional areas as d scribed above, nly ne cross-sectional area is included.

Th plates 26 are stacked to form th growth chambers. Preferably, the plates are spaced 1 mm apart or greater. Although the plates may be spaced closer to one another, air bubbles tend to become trapped between the plates and interrupt the even flow of medium when spaced less than 1 mm apart. The surfaces of the plates may be roughened, corrugated, convoluted or otherwise irregular to increase their surface area and the number of cells capable of growing on a given plate. If irregular, the 1 mm spacing between the plates should be between the facing peaks of irregular surfaces. The surfaces of the plates also may be surface treated in a variety of different ways to promote cell growth. Typical treatments include carboxyl group treatments, collagen treatments, fibronectin treatments or feeder cell layers.

The plates according to the preferred embodiment were molded from K-resin, a block co-polymer of polystyrene and butadiene, sold by Phillips Chemical Co., Bartlesville, OK, 74004. Suitable plate materials include styrenic materials or materials such as polymethyl pantene. However, the plate may be of virtually any material that is sufficiently strong, nontoxic, biocompatible, and otherwise suitable for tissue culture.

The plates of the embodiment of FIGS. 2-4 have a novel construction which facilitates flow distribution and manufacture. Each plate 26 has an upper surface 30 bounded by a peripheral wall 32 (Fig. 3). The inside facing surface 34 of wall 32 along with the plate upper surface 30 define the side walls and floor of a growth chamber 24. When the plates 26 are stacked in the assembled device, the top edge 35 of wall 32 mates and seals with the lower surface 36 of the adjacent plate to define a growth chamber, the ceiling of the chamber being defined by the lower surface 36 of the adjacent plate. To facilitate the mating arrangement of the stacked plates, the wall 32 is provided on its top edge 35 with a groove 33 for receiving a mating ridge 37 on the bottom surface of an adjacent plate. The mating ridge 37 and groove 33 align the stacked plates.

The four corners 38,38 and 40,40 of each plate 26 are solidly filled-in to a thickness equal to the height of the peripheral wall 32. The filled corners add support to the assembled structure. The filled corners further reduce the potential for fluid turbulence and "dead spots," as will be explained more fully below.

Each plate 26 has a bore at diagonally-opposed, filled corners 40. In the assembled condition, the bores 42,44 of the stacked plates 26 are axially aligned and f rm the inlet and outlet manif lds 20,28, respectiv ly. A passag 48 xt nds from ach bore 42,44 through th filled corn rs 40 to the interior space defined by the sid walls and floor of each plate 26. These passag s in the assembl d v ssel form th fluid restriction ports 22, 23 providing fluid access between the manifolds 20,28 and the growth chambers 24. Each passag has a floor defined by a p rtion of the upper surface 30 of the plate 26 and sidewalls 49 formed integrally as part of the corners 40. The height of each passage equals the height of the peripheral wall 32. The fluid restriction ports 22, 23 are formed when the flat bottom surface of an opposing plate 26 is stacked to seal the open upper extremity of the passage 48.

The particular shape of the fluid restriction port in the preferred embodiment includes a narrowed internal portion, as at constriction 50. The width of the flow restriction port 22 increases continuously and substantially from constriction 50 in a direction toward the growth chamber 24. This arrangement causes medium entering the growth chamber to flare-out and be evenly dispersed in a fan pattern into the growth chamber space, promoting nutrient supply and even fluid flow across the entire growth surface. This arrangement also reduces turbulence, especially at and around the restriction ports 22. In the embodiment shown, the width of the flow restriction port increases linearly while the height remaining constant. However, a port shaped as a second or third order venturi would provide for continuous, gradual change in velocity, thereby further promoting nonturbulent flow.

The nonturbulent and directional flow pattern is further facilitated by the filled corners 38 and by flow-guiding ribs 46. The corners, if not filled, would define areas remote from the direction of flow, which in turn would result in turbulence and "dead spots," that is, areas within the growth chamber which do not receive a continuous and directional flow of fresh media so as to cause cell death. The filled corners provide a baffle which acts to channel flow continuously in the direction of the outlet ports. The ribs 46 provide a dual function. They serve to provide structural support to each plate maintaining the plates at the proper spacing, even when draining the device under a vacuum, and also may be positioned to channel flow continuously in a direction toward the outlet ports.

To assemble the device, the plates must be stacked and secured to one another in a manner to hermetically seal the peripheral walls and corners of the plates to one another. In this embodiment each plate is welded to an adjacent plate by ultrasonic welding. However, any method of fabrication such as solvent welding, RF welding, potting, glue or even gaskets would be acceptable, so long as the final product has sufficient strength and is nontoxic to cultured cells.

In op ration, th device first is seeded with cells. Th n, fluid m dia is suppli d to th attached cells as follows. Fluid medium is introduced into inlet manifold 20 via inlet conduit 16. The fluid medium then passes

through the various flow restriction ports 22 into the associated growth chambers 24. Because of the overall construction of the flow restriction ports and the growth chambers, flow is distributed continuously and thoroughly to all surfaces of the growth chamber 24, the fluid medium always moving generally in a direction toward the outlet flow restrictors 23. The medium then passes through the outlet flow restrictors 23, into the outlet manifold 28 and then out of the device via the outlet conduit 18.

Another embodiment of the device comprises a cylindrical casing containing an array of longitudinally oriented culture chambers. As shown in Fig. 5, a cylindrical casing 56 encloses and is sealed to the outside surface of a cylindrical culture chamber 57. The casing 56 is sealed at each end with two circular end plates, inlet end plate 58 and outlet end plate 59, each of which is spaced slightly from the opposite ends of the culture chamber 57. The spacing between the inlet end plate 58 and the inlet end of the culture chamber 57 defines an inlet manifold 60. The spacing between the outlet end plate 59 and the outlet end of the culture chamber 57 defines an outlet manifold 62. Fluid enters the inlet manifold 60 via an inlet conduit 64 which is fluidly attached to and extends axially from inlet end plate 58. Fluid exits the outlet manifold 62 via an outlet conduit 66 which is fluidly attached to and extends axially from outlet end plate 59.

The longitudinally extending growth channels of the culture chamber 57 are formed by rolling a rectangular, flexible sheet 72 formed with a plurality of longitudinally-oriented, projecting ridges 74. Upon rolling the sheet from a side parallel to the projecting ridges 74, the sheet 72 assumes the shape of a spiral cylinder (Fig. 6). The projecting ridges 74 along with the overlapping turns of the rolled sheet 72 define a longitudinal array of channels 76, the height of the ridges 79 defining the height of each channel 76. The open ends of the channels 76 are plugged or capped to provide restriction ports 22, limiting fluid access to each channel 76.

The operation of this embodiment is similar to that described above. First the device is seeded with cells which are allowed to attach to the surfaces of the channels 76. Then, fluid medium is introduced via the inlet conduit 64 into inlet manifold 60. Fluid medium then passes from the manifold into the longitudinally extending growth chambers 76 via the inlet restriction ports 22. The fluid medium passes continuously along the length of the growth channel 76, passes through the outlet restriction ports (not shown) and exits the device via the outlet manifold 62 and outlet conduit 66.

According to one aspect of the invention, the cell culture vessel of the invention is provided as part of an assembly 80 as depicted schematically in Fig. 7. The assembly 80 is constructed and arranged for continuous operation. The assembly 80 is a closed-loop system connecting the culture vessel 10 of the invention with a fluid reservoir 82. An outlet port 84 of the reservoir 82 is connected to the inlet port 86 of the culture vessel 10 via a fluid supply conduit 88. The outlet end 90 of the culture vessel 10 is in fluid communication with an inlet port 92 of the reservoir 82 via fluid return conduit 94. A pump 96 is positioned along the fluid supply conduit 88 for continuously pumping fluid medium from the reservoir through the culture vessel 10. A nutrient supply line 98 is fluidly connected to the fluid supply conduit 88 between pump 96 and vessel 10 such that nutrients may be added to the fluid supply conduit 88. A pump 100 is provided for pumping the nutrients into the fluid supply conduit 88. The reservoir 82 also is provided with a product withdrawal conduit 102 connected to a withdrawal pump 104 for removing fluid downstream of the culture vessel, preferably continuously. Finally, the assembly is provided with probes 106 on the fluid supply conduit 88 and the fluid withdrawal conduit 94. These probes 106 provide means for sensing the condition of the medium. These probes may be connected to a control device 108 which in turn is connected to the various pumps for controlling the introduction of nutrients and withdrawal of products from the reservoir based upon the condition of the medium. Optionally, oxygen exchange means 110 may be provided for continuous resupply of oxygen to the culture medium. Preferably, the nutrient supply pump 100 and the product withdrawal pump 104 are operated continuously and at the same rate such that resupply medium is continually being introduced and product is continually withdrawn from the system, the rate of pumping being determined by the control means.

As discussed above, it is not necessary that the flow restriction ports be of a uniform size. If uniform flow through each chamber is desired, then, generally speaking, it is necessary that the flow restriction ports be of the same dimensions. However, it will be understood that flow will depend not only upon the size of the flow restriction port, but also on the particular dimensions of the growth chamber. Thus, the relative size of the flow restriction port and growth chamber together may be varied while maintaining a particular flow rate.

In the embodiments illustrated, only one pair of restriction ports per growth chamber has been described. It is, of course, possible to have many flow restrictors on the inlet or the outlet side. One inlet and one outlet restriction port may be preferred as they facilitate manufacture, lessen turbulence, and reduce the lack of cell growth normally found at and very close to the flow restriction ports.

It further will be understood by one of ordinary skill in the art that it is possible to have flow restriction ports on the inlet side only. A vessel of such construction may be preferred for applications requiring the recovery of cells from the vessel, as conventional methods for removing cells from culture vessels tend

t yi ld cell clumps which may clog a constricted outl t. It also is possibl to have restriction ports on the outlet sid only. Th mbodiment f FIGS. 9-17 includes nly the inl t constrictions ports.

It further is preferred that the sum of the cross-sectional areas of the flow restriction ports be less than or equal to the cross-sectional area of the outlet conduit. Otherwise, the outlet conduit will set up a back-pressure which may result in preferential flow through one or more growth chambers.

In FIG. 8, another embodiment of cell culture vessel similar to that depicted in Figs. 2-4 is shown, formed of a series of flat plates sandwiching gaskets, the gaskets forming the side walls and restriction ports of the growth chambers. In this embodiment, the plates 126 have substantially flat upper and lower surfaces. A transverse bore 128 is located at each of a pair of opposing corners 129 of each plate. The gasket 130 has a perimeter corresponding in size and shape to the perimeter of the plates 126. The interior facing walls 132 of the gasket 130 define a hollow space. When a pair of plates 126 sandwiches a gasket 130, the facing surfaces of the plates 126 form the upper and lower extents of a growth chamber, while the interior facing walls 132 of the gasket form the side walls of the growth chamber.

The corners 134 of the gasket are filled. A pair of opposing corners each has a gasket bore 136 extending therethrough, these gasket bores 136 corresponding in size and shape to the bores 128 at opposing corners 129 of the plates 126. A passage 138 extends from the gasket bore 136 inwardly through the corner to the interior space defined by the inwardly facing walls 132 of the gasket 130. When a pair of plates 126 sandwiches a gasket 130, the bores 128 of the plates 126 and the gasket bores 136 align to form manifolds. The passage 138 is closed off on upper and lower extents by the stacked plates to form the restriction ports.

An assembly of such stacked plates and gaskets may be held together by a compressive force, such as by clamps. This particular embodiment of the invention has as an advantage the ability to separate the plates from one another after cells have been grown. This allows a monolayer of cells or "skin" to be peeled from the surface of the plates and otherwise facilitates access to the cells on the surface of a plate.

In FIG. 9 another embodiment of a cell culturing assembly is shown that functionally is the same as the embodiment shown in FIG. 1. The assembly differs from that of FIG. 1 in the manner in which the array of plates are held together. The assembly 200 shown in FIG. 9 includes inlet and outlet conduits 202 and 204 respectiv ly, a stack of plates 206 and a fram 208 that holds th stack of plates tog ther and h rm tically seals th stack of chambers f rmed betw n them. In FIG. 10, nly a few of the stack of plates are shown sealed within the frame 208, but it sh uld be appreciated that as many as 25 or 50 plates may be stack d on upon an ther to form a corresp nding numb r f chamb rs.

In FIGS. 11-17, one plate 212 that may be used in the stack of FIG. 10 is shown but it is to be understood that other plates such as shown in FIGS. 3 and 4 may be used instead. The frame 208 is not limited to just one plate configuration. At opposed corners 214 and 216 inlet and outlet ports 218 and 220 are provided which correspond to the ports 42 an 44 in the embodiment of FIGS. 3 and 4. A thickened rim 222 extends about the four sides of the plate from each surface thereof and surrounds the thin major portion 224 of the plate (see FIGS. 11-13). The rim 222 is spaced inwardly from the outer edge 226 of the plate to define a tongue 228 whose function is described below.

The two surfaces of the plates are substantially identical except for aligning risks in two corners as described below.

The ports 218 and 220 extend through the thin major portion 224 of the plate, and a pair of V-shaped ribs 230 and 232 disposed on each side of port 218 define a restricted flow path 234 between the adjacent apexes of the V-shaped ribs 230 and 232. No restricted passage is formed adjacent the outlet port 220 that corresponds to the restricted passage 234.

At the other pair of opposed corners 240 and 242, diagonal ribs 244 and 246, respectively, connect adjacent portions of the rim 222 and define baffles in the chambers so as to eliminate the so called "dead spots" in the corners of the chambers remote from the flow path between the inlet and outlet ducts 218 and 220. These ribs essentially perform the same function as the fill at the opposed corners in FIGS. 3 and 4. In FIGS. 11 and 12, the top and bottom surfaces of the plate 212 are shown, and it is evident from them that the two surfaces of the plates as thus described are essentially identical. Therefore, when two identical plates are placed face to face, the rims 222 stack one upon another as shown in FIG. 10 and the ribs 230, 232, 244 and 246 engage one another to form walls that in part define the growing chambers between the plates. Similarly, the transversely extending ribs 248 that correspond to the ribs 46 in the embodiment of FIGS. 3 and 4 register with one another to direct flow through the chamber.

In the opposed corners 240 and 242 of the plate 212 stacking ribs 250 and 252 are provided on one face of the plate while corresponding troughs 253 and 254 are formed on the opposite face thereof. Cross-sections of the ribs and troughs are shown in FIGS. 16 and 17. It will be noted in the cross-sectional views that the troughs are slightly longer than th ribs s as to assist in centering the plates on upon an ther. It will be appreciated that because th ribs 250 and 252 and troughs 253 and 254 at the pposite corn rs are disposed at an angle to on another, the troughs and

ribs prevent the plates from being stacked in any way but with inlet and outlet ports 218 and 220 of each plate properly aligned at the same corners of the stack. Moreover, the ribs and troughs will serve to hold several plates in the precise alignment with one another before the frame 208 is molded about them.

In the previously described embodiments no special frame is illustrated for holding the array of plates together and hermetically sealing the chambers, and various methods are suggested for assembling the array of plates, such as ultrasonic welding, solvent welding, potting etc. In this embodiment, the array of plates are held together by frame 208. Very substantial savings in manufacturing costs are derived from this system as well as a better seal for each chamber 211 and an aesthetically superior product is achieved as compared to the vessel manufactured by the other techniques described. The frame is molded by placing the stack of plates in a tool cavity and injecting the styrenic material from which the frame is made into the cavity to form it. It will be noted in FIGS. 9 and 10 that the frame material completely encloses the tongues 228 and fills the cavity 260 between adjacent tongues to the interface of the adjacent rims 222. The frame totally encloses the edges of each of the identical plates in the stack and extends around the outer edges of the end plates in the stack. This technique which is commonly called insert molding not only bonds the frame 208 to the plates but also forms a mechanical interlock between the plates may be so that the assembly cannot fall apart. The principle advantage of this assembly is that all of the individual plates may be secured together in a single molding step as opposed to the separate steps required by the other techniques to attach each of the individual plates together. The importance of this feature will be particularly appreciated when it is realized that as many as 25 or 50 plates may be stacked in a single assembly, and the perimeter of each plate may be approximately 36 inches. Therefore, in a stack of 50 plates, approximately 150 linear feet of seal must be provided about the chambers. Furthermore, in many applications, so long as the frame 208 holds the stack together and seals with the end plates, a failure of a seal between adjacent inner plates will not be catastrophic for the frame will prevent the loss of any fluid from the system and the only exit for the fluid is the outlet conduit 204.

In FIG. 10, it will be noted that the outer face of the topmost plate in the stack does not have the same configuration as the inner face. However, the inner face is identical to the lower faces of the plates below to form a chamber 211. Similarly, only the top face of the lower plate (not shown) is configured to form a chamber 211.

While polystyrene has been suggested as the material from which the frame may be made, it will be appreciated that other materials may be used as well so long as they are compatible with the function performed by the assembly. For example, the frame could be injection molded from a rubber-like styrenic material which would provide physical protection for the assembly if it is dropped or otherwise subject to a sharp impact.

As suggested above, the plates may typically be approximately 9 inches square, and a very substantial number of plates may be used in a single assembly to form as many as 25 or 50 chambers. In such a construction, the wall thickness of the frame measured to the outer edges of the tongues may be approximately 3/32 inch, and the outer flange 270 of the frame over the outer surfaces of the end plates as shown in FIG. 10 may be approximately 3/16 inch. Because the frame is continuous, it permanently and securely bonds the stack together so that the plates cannot accidentally separate nor can any leakage occur from the system so long as the bonds between the frame and the outer surfaces of the end plates are secure.

It should be understood that various changes and modifications of the embodiments described may be made within the scope of the invention. It is intended that all matter contained in the above description or shown in the accompanying drawings shall be interpreted in all illustrative and not limiting sense.

Claims

1. A tissue culture plate assembly comprising:
   a plurality of plates stacked one upon the other with adjacent plates defining growth chambers between them, the plates having edges which are aligned with one another in the stack,
   inlet and outlet conduits connected to the stack for channeling fluid to and from the chambers,
   and a frame enclosing the edges of all the plates, hermetically sealing the chambers and mechanically interlocking the stacked plates together.

2. A tissue culture plate assembly, including a stack of chambers comprising:
   a plurality of parallel plates disposed in alignment adjacent one another and defining chambers between them, the plates having edges which are aligned with one another,
   and a frame enclosing the edges of all the plates for sealing the chambers and mechanically interlocking the plates.

3. A tissue culture plate assembly as defined in claim 1 or claim 2 wherein the frame is molded as a unitary structure about all the edges of all the plates.

4. A tissu culture plat assembly as defined in any of claims 1-3 wh r in th plates in th stack are identical with ne anoth r.

5. A tissue culture plate assembly as defined in any of claims 1-4 wherein each of the plates has a rim adjacent the edge and which extends about the periphery thereof, the rims of adjacent plates being stacked one on the other and providing side walls for the chambers.

6. A tissue culture plate assembly as defined in any of claims 1-5 wherein tongues are formed in the edges of the plates with the tongues of adjacent plates in the stack forming cavities between them, said frame filling the cavities between the tongues and preferably bonding the plates together.

7. A tissue culture plate assembly as defined in any of claims 1-6 wherein each of said plates has inlet and outlet ducts that communicate with the inlet and outlet conduits to direct fluid through the chambers.

8. A tissue culture plate assembly as defined in claim 7 further including restricted passages provided in each of said plates and connecting the inlet duct to the chambers on each side of each of said plates.

9. A tissue culture plate assembly as defined in claim 8 further including ribs provided in a plate adjacent the inlet duct to define the restricted passages.

10. A tissue culture plate assembly as defined in any of claims 1-9 further including stacking ribs and grooves on opposite faces of each of the identical plates for aligning the plates with one another in a preselected relationship.

11. A tissue culture plate assembly as defined in any of the preceding claims wherein the chambers are at least 1 mm in height.

12. A tissue culture plate assembly as defined in any of the preceding claims wherein the plates are substantially square.

13. A tissue culture plate assembly as defined in any of the preceding claims wherein support ribs separate adjacent plates in the chamber.

14. A tissue culture plate assembly as d fined in claim 1 or claim 2 wh rein protrusions are formed in th dges of th plates with the protrusions f adjacent plates in the stack forming cavities between them, said frame filling the cavities between th protrusions and bonding the plates togeth r.

15. A tissue culture plat ass mbly as defin d in any of the preceding claims wherein the frame contacts all of the edges of each plate.

16. A tissue culture plate assembly as defined in any of the preceding claims comprising at least 25 plates.

17. An assembly defining a stack of chambers comprising:

a plurality of parallel plates disposed in alignment adjacent one another and defining chambers between them, the plates having edges which are aligned with one another,

and a frame enclosing the edges of all the plates for sealing the chambers and mechanically interlocking the plates.

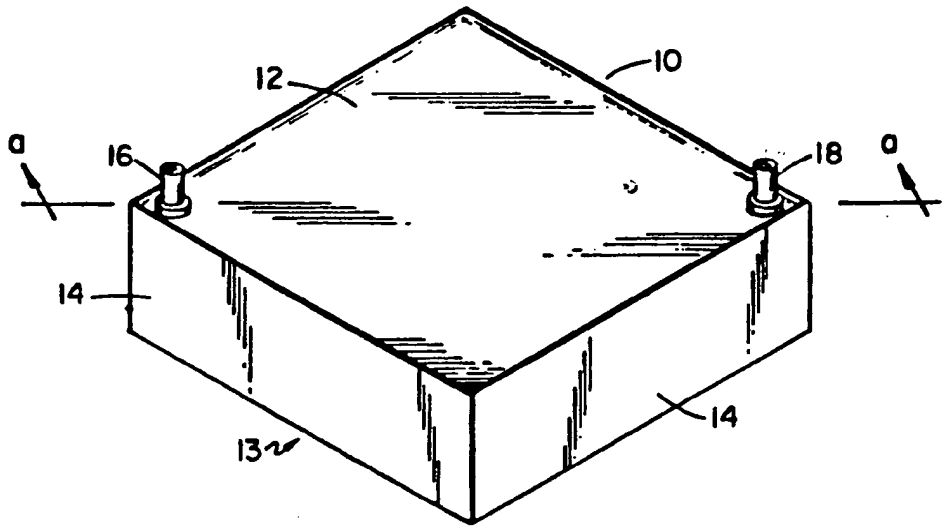

FIG. 1

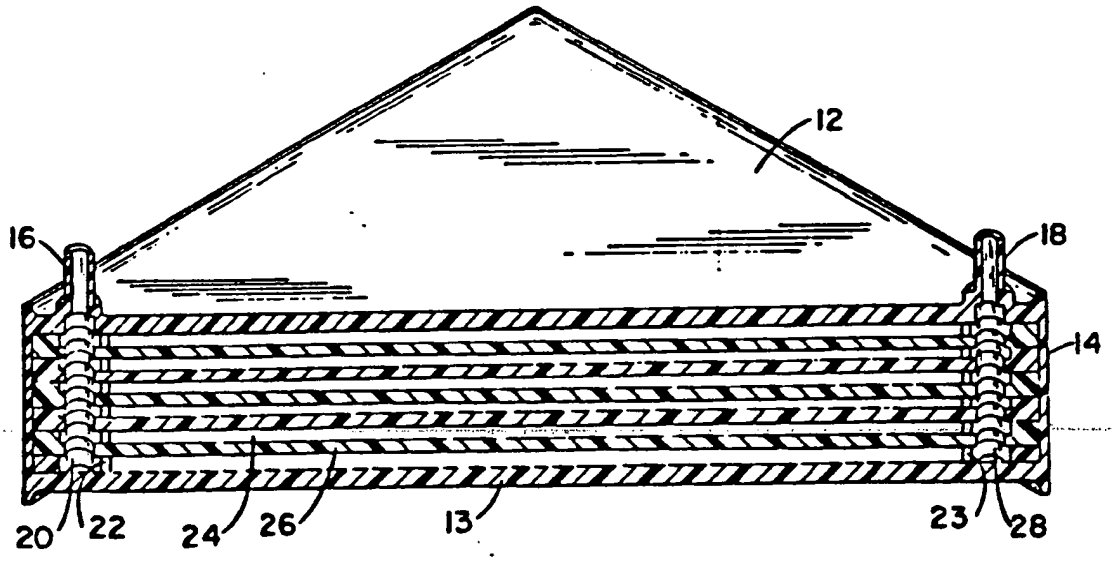

FIG. 2

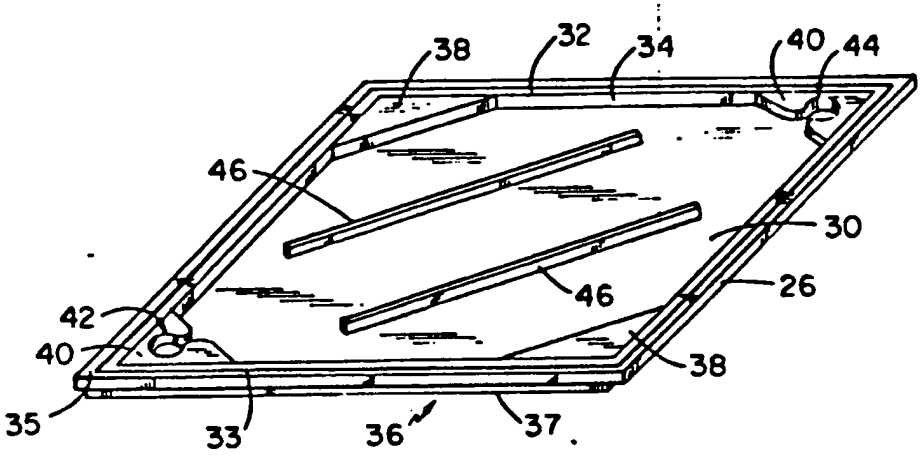
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FIG. 3

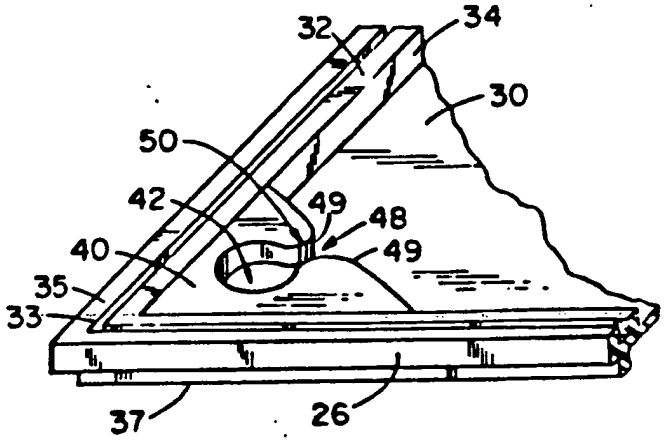
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FIG. 4

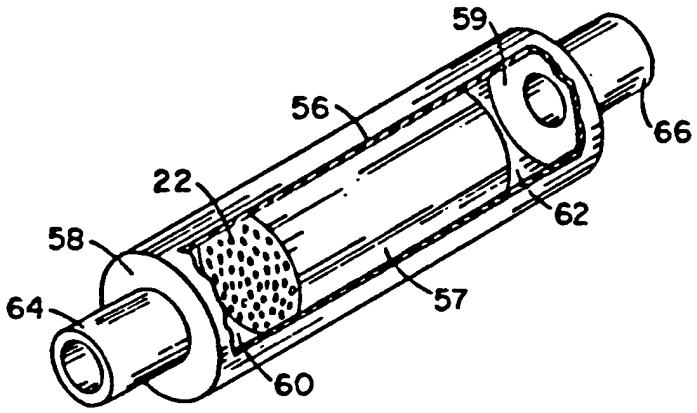

FIG. 5

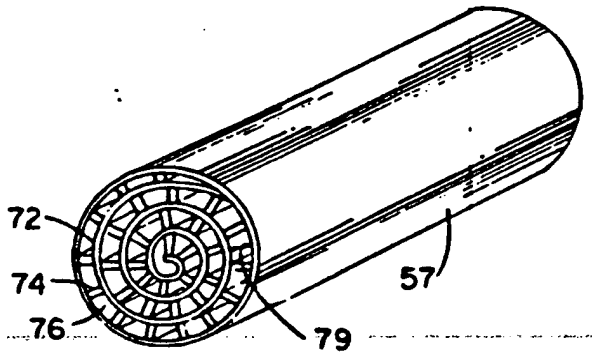

FIG. 6

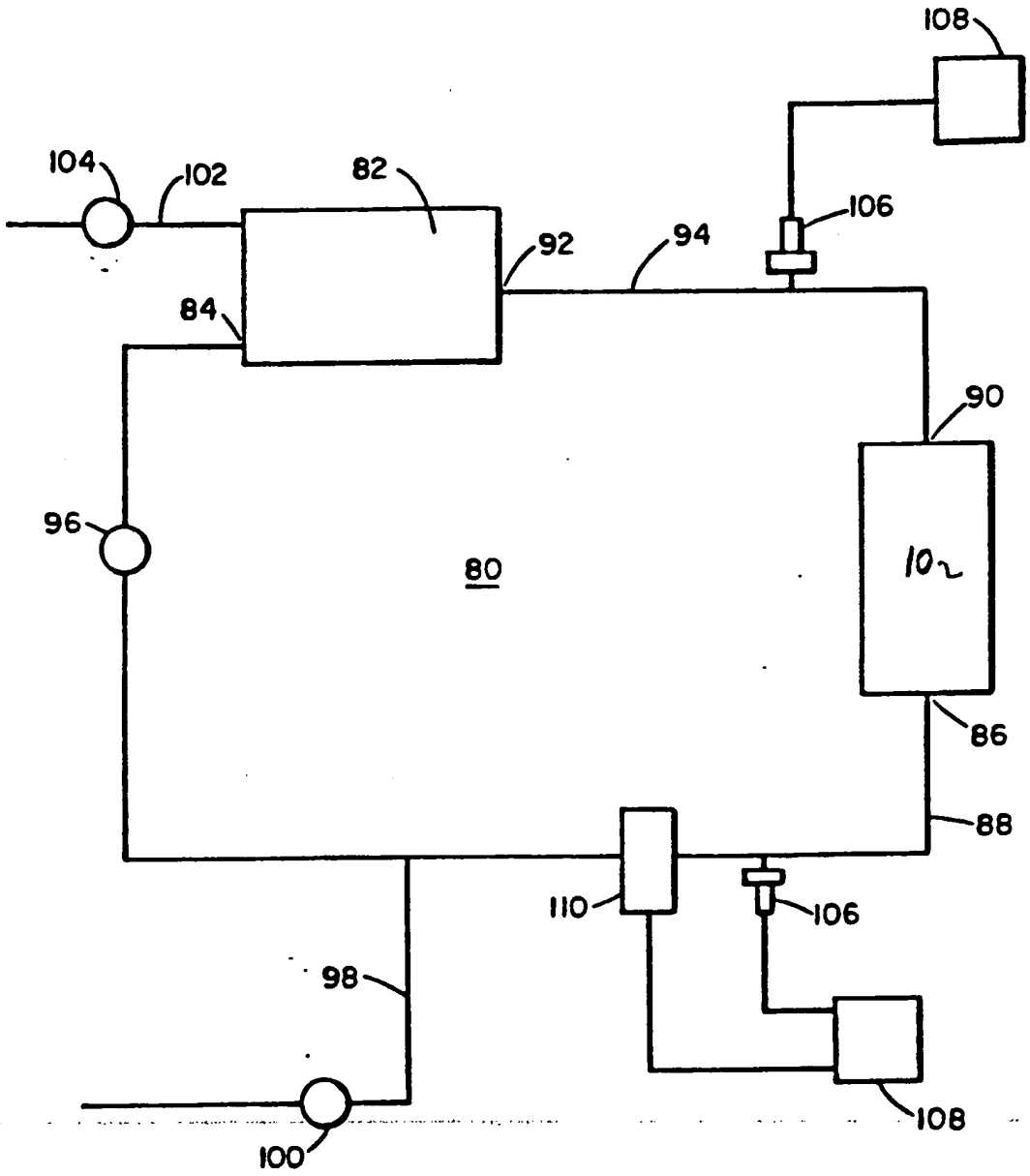

FIG. 7

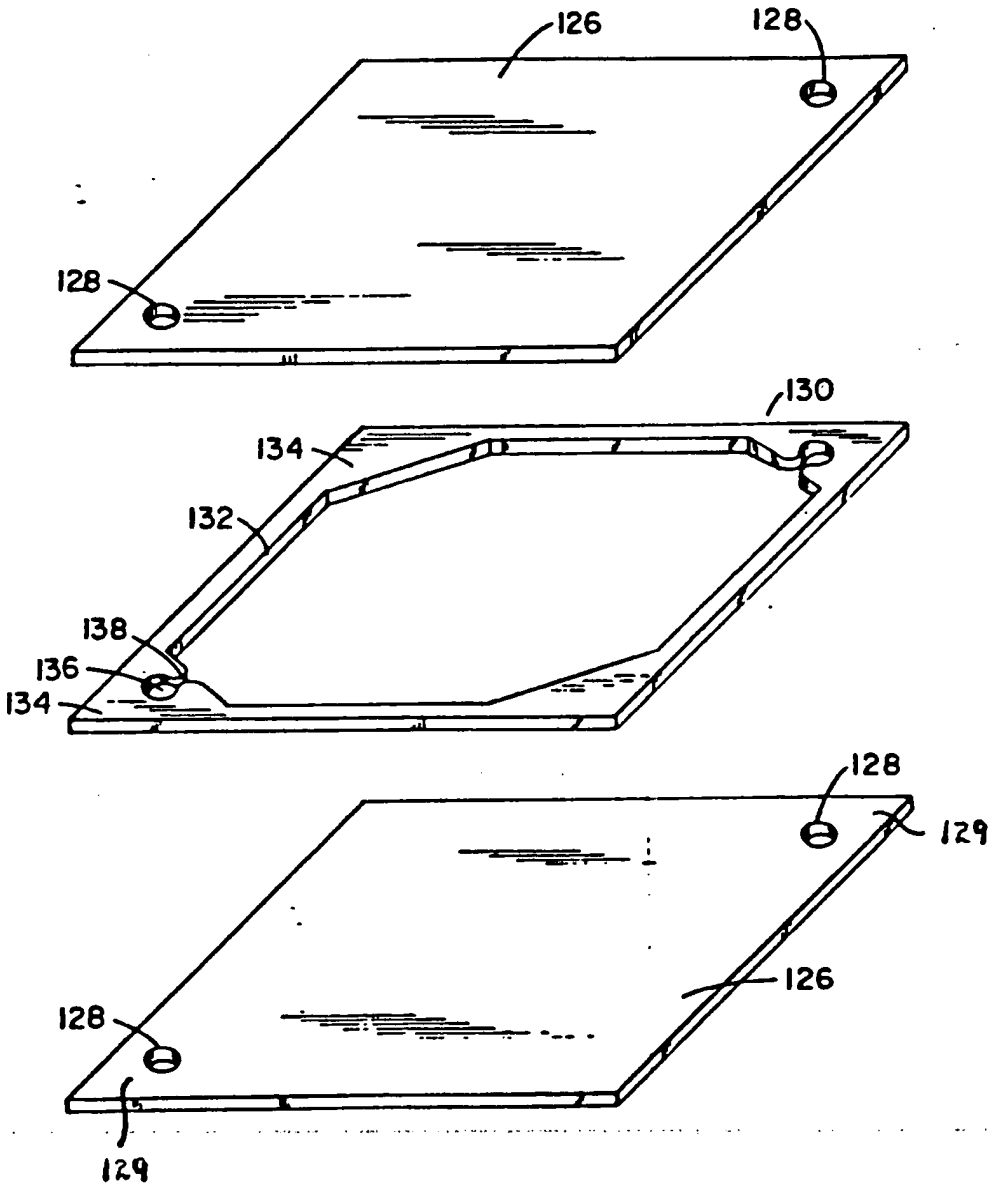

FIG. 8

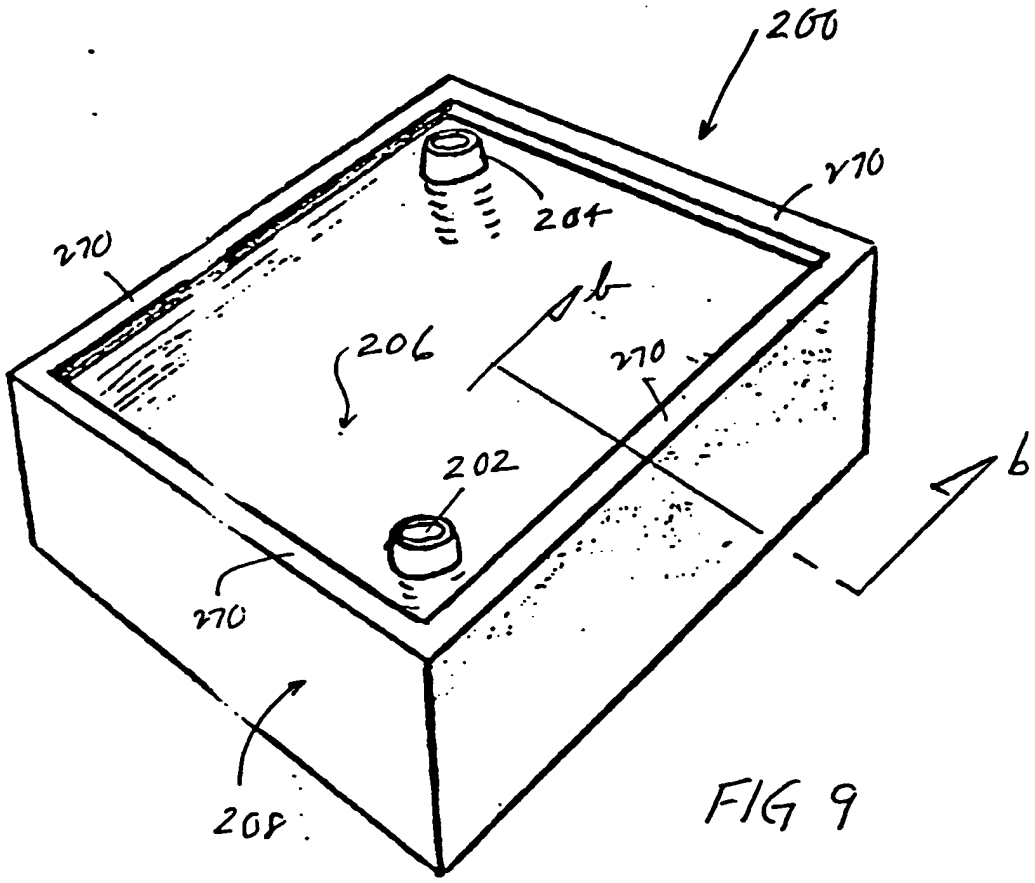

FIG 9

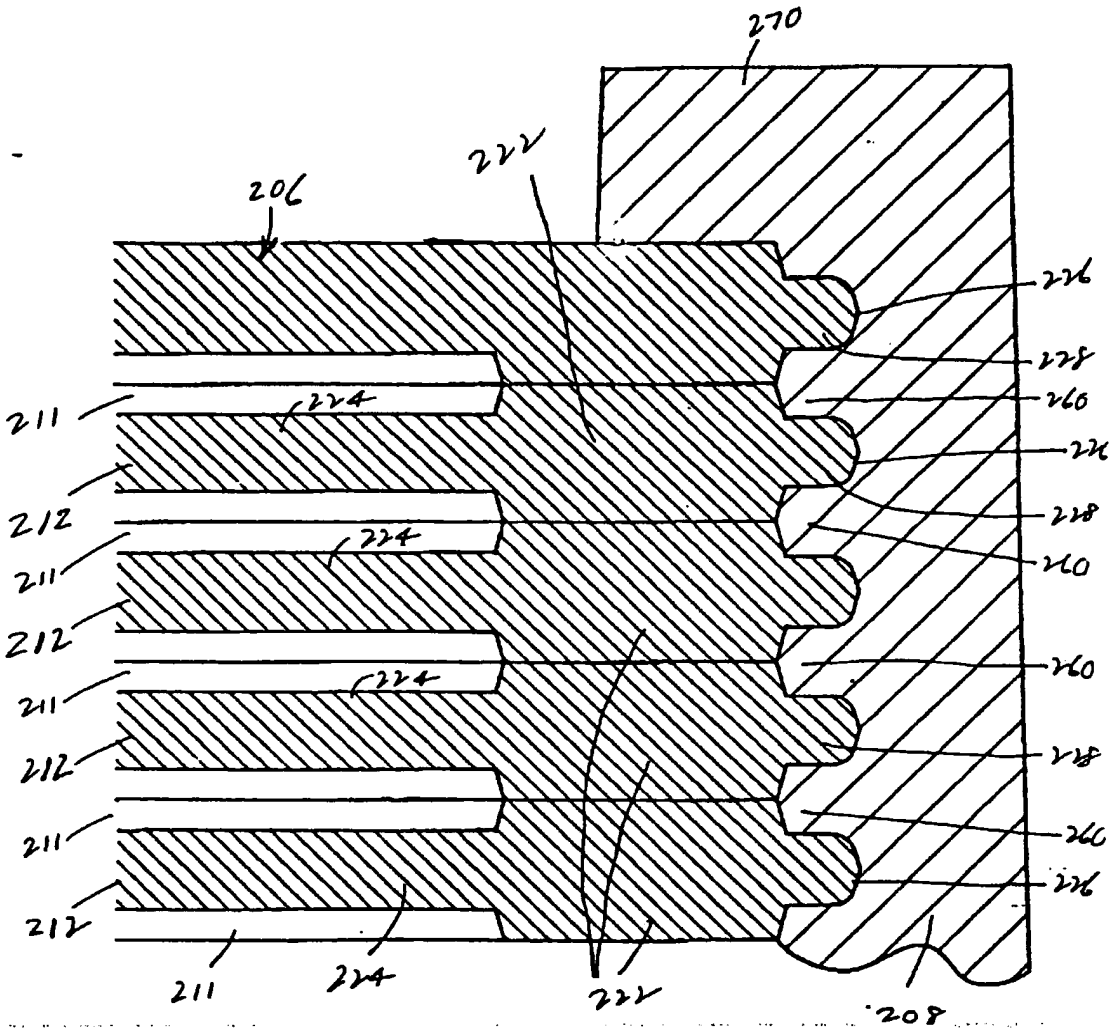
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FIG. 10

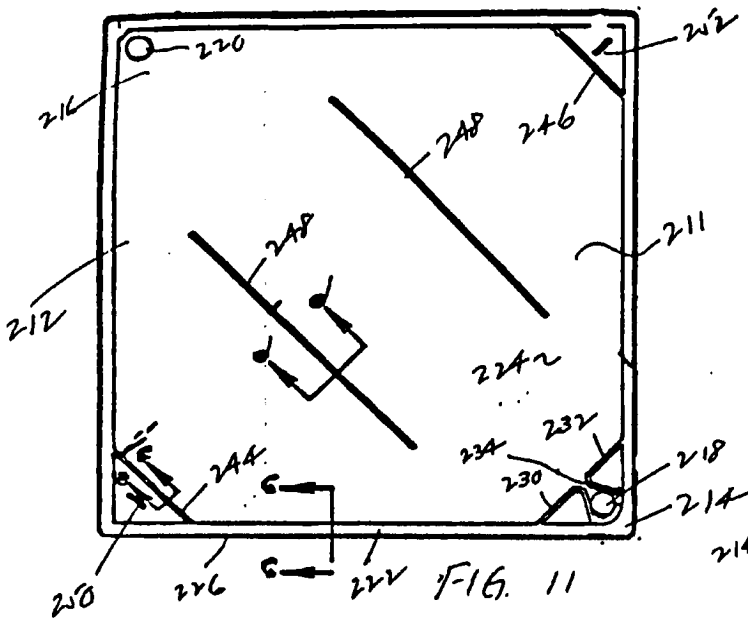

FIG. 11

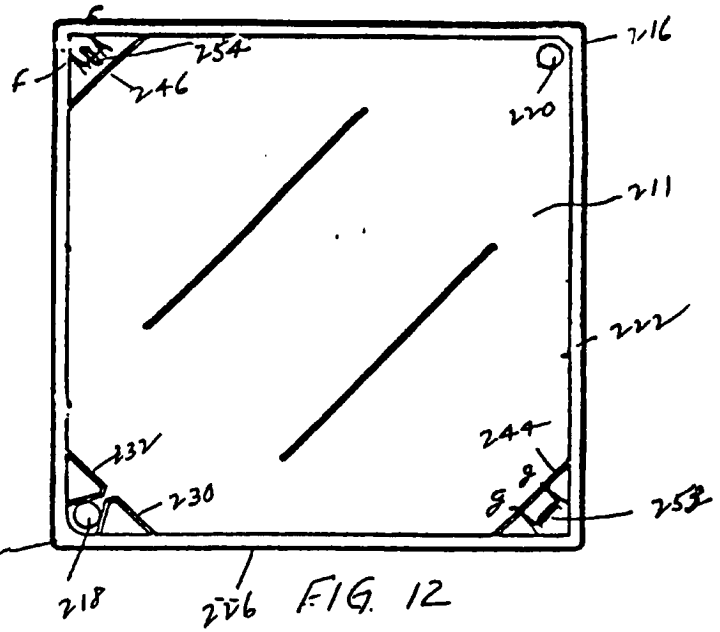

FIG. 12

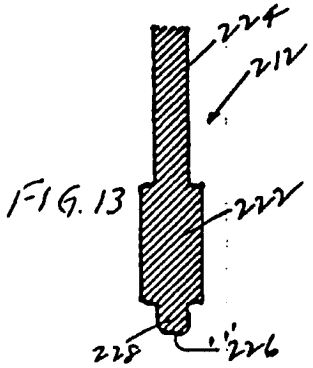

FIG. 13

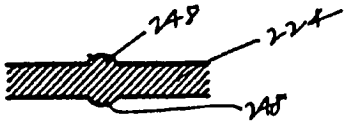

FIG. 14

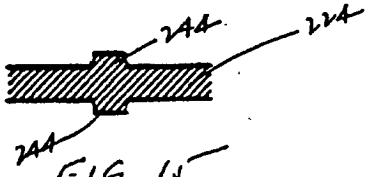

FIG. 15

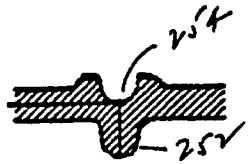

FIG. 16

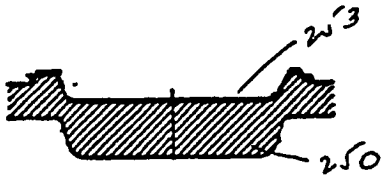

FIG. 17